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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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MUETING, RAASCH & GEBHARDT, P.A.
P.O. BOX 581415
MINNEAPOLIS, MN 55458

EXAMINER	
MOORE, WILLIAM W	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 04/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,330	TRAVIS ET AL.	
	Examiner	Art Unit	
	William W. Moore	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,18-29 and 31-38* is/are pending in the application.

4a) Of the above claim(s) *33-35* is/are withdrawn from consideration.

5)☒ Claim(s) *18,20,24 and 36-38* is/are allowed.

6)☒ Claim(s) *1-16,19-23,25-29,31 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *33-35* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Applicant's amendments to claims 1, 8, 11, 14, 16, 18-27, and 29 and the new claims 31-38 filed December 15, 2004, have been entered and claims 17 and 30 were canceled at Applicant's request. The amendments overcome the rejections of record of claims 18, 20, and 24 herein and overcome the rejection of record of claim 16 under 35 U.S.C. § 112, second paragraph. The new claims 36-38 present none of the issues that require the rejections of record and claims 18, 20, 24 and 36-38 are allowed herewith. The Declaration filed December 15, 2004, under 37 CFR 1.131 by the three co-inventors herein has been considered and is persuasive in establishing that U.S. Patent No. 6,444,799 to Ross, of record, cannot be applied as prior art to an invention of claims 1-16, 18-29, 31, 32, and 36-38 herein. Claims 17 and 30 were canceled at Applicant's request, thus claims 1-16, 18-29 and 31-38 are now pending.

Election/Restrictions

Newly submitted claims 33-35 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

The inventions of claims 1-16, 18-29, 31, 32, and 36-38, on the one hand, and the inventions of claims 33-35, on the other hand, are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are not disclosed to be capable of common use where no particular agent recited in methods or kits of claims 33-36 need function as an inhibitor of any particular species of the genus of polypeptides defined by as much as a 67% amino acid sequence divergence from the disclosed amino acid sequence set forth in SEQ ID NO:1 herein and the examined products of claims 1-16, 18-29, 31, 32, and 36-38 have different modes of operation, different functions, and different effects than the methods and kits of claims 1-16, 18-29, 31, 32, and 36-38.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 33-35 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16, 19-23, 25-29, 31, and 32 are for reasons of record rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is essentially the rejection of record save for exclusion of claims 18, 20, 24 and 36-38 and claims withdrawn from consideration. Applicant's arguments filed December 15, 2004, have been fully considered but they are not persuasive. Applicant suggests at pages 12-13 of the remarks accompanying the claim amendments, that a requirement for a specific function, "amidolytic activity for cleavage of a nondenatured human α_1-protease inhibitor at [its] reactive site loop region", in a claimed protease polypeptide, or in a protease polypeptide product of a claimed encoding nucleic acid, might somehow recite subject matter an artisan would have considered Applicant to have possessed when the specification was filed if the protease functionality were combined with either or both of an appellation of source, i.e. "isolated from *Porphyromonas gingivalis*", and non-specific indications of structure, e.g., as much as 63% amino acid sequence non-identity in a polypeptide by comparison with all or part of the amino acid sequence set forth in SEQ ID NO:1 and as much as 50% non-identity in an encoding nucleic acid by comparison with the nucleic acid sequence set forth in SEQ

ID NO:2 so long as the encoded amino acid has no more than 63% amino acid sequence non-identity in a polypeptide by comparison with all or part the amino acid sequence set forth in SEQ ID NO:1. Applicant also urges that the various physical and inhibitor substrate limitations recited in the claims might be somehow be embodied by the myriad members of the genus of polypeptides having such little structural similarity to the sole disclosed protease.

Yet Applicant cannot point out a single species of protease having such widely-divergent structure anywhere in the disclosure, nor any protease having a structural divergence intermediate between the disclosed amino acid and nucleic acid sequences and the claimed structures, that has the claimed function. The specification discloses but a single protease having the requisite activity and neither exemplifies nor describes Applicant's preparation, or isolation from *Porphyromonas gingivalis*, of proteases having such widely-divergent structures nor any nucleic acid molecules comprising a coding sequences specifying proteases having such divergent structures. The specification does not suggest even one of the numerous locations in the sequence of SEQ ID NO:1 wherein amino acid sequences alteration permitted by the claims might occur, or what the alteration might be. The specification does not otherwise disclose or suggest the nature or source of such generic proteins meeting the functional limitations of the claims. "While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. §112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). The rejection of record of claims 1-16, 19-23, 25-29, 31, and 32 is sustained because the specification provides no relevant identifying characteristic of the widely divergent proteases that might exhibit the recited activity, and fails to identify any characteristics that might permit a correlation

between undisclosed structures of the myriad proteases and nucleic acid sequence of the rejected claims and the disclosed amino acid sequence of SEQ ID NO:1.

Claims 1-16, 19, 21-23, 25-29, 31, and 32, are for reasons of record rejected under 35 U.S.C. § 112, first paragraph, because the specification is not enabling for any embodiment of protease having an amino acid sequence that diverges from the amino acid sequences of any of SEQ ID NO:1 by amino acid substitutions, deletions and insertions, or combinations thereof at as many as 67%, or even 48%, of the 696 amino acid positions of SEQ ID NO:1 from position 148 through position 843, inclusive. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, make and use the invention commensurate in scope with these claims.

This is essentially the rejection of record save for exclusion of claims 18, 20, 24 and 36-38, and exclusion of claims 33-35 withdrawn from consideration, Applicant's arguments filed December 15, 2004, have been fully considered but they are not persuasive. Applicant suggests at pages 13-15 of the remarks accompanying the claim amendments, that a requirement for a specific function, "amidolytic activity for cleavage of a nondenatured human α_1-protease inhibitor at [its] reactive site loop region", in a claimed protease polypeptide, or in a protease polypeptide product of a claimed encoding nucleic acid, might somehow recite subject matter that one of skill in the art could have made and used according to guidance in the specification if the necessary functionality is combined with non-specific indications of structure, e.g., as much as 63% amino acid sequence non-identity in a polypeptide by comparison with all or part of the amino acid sequence set forth in SEQ ID NO:1 and as much as 50% non-identity in an encoding nucleic acid by comparison with the nucleic acid sequence set forth in SEQ ID NO:2 so long as the encoded amino acid has no more than 63% amino acid sequence non-identity in a polypeptide by comparison with all or part the amino acid sequence set forth in SEQ ID NO:1. There is no such guidance that Applicant can point to in the specification for making such divergent, yet functional, proteases, either by altering them after isolation from *P. gingivalis* or designing them *de novo*, yet Applicant

urges that a method of making one of the myriad embodiments embraced by the claims, the embodiment disclosed in SEQ ID NO:1, somehow constitutes a method of making the myriad other embodiments that diverge widely in their amino acid sequences from that disclosed in SEQ ID NO:1 yet retain an ability to recognize and cleave the active site loop of the human α_1-protease inhibitor.

The specification does not teach which amino acid sequence positions must be retained to permit a protease to recognize the target inhibitor. Neither the specification nor the prior art of record describe how the artisan might start with the target of a protease and design *de novo*, in reverse, an amino acid sequence providing a structure that permits a polypeptide to contact, recognize, and specifically cleave anything. Applicant can point to no "objective truth" in the specification, or in prior art of record, that currently guides artisans to such feats of reverse-engineering, leading eventually to a product that falls within the structural limitations of the claims and the specification provides no guidance for the introduction of 438 amino acid sequence alterations in SEQ ID NO:1 from position 148 through position 843, inclusive, satisfying a statistical limitation of 37% identity, or even 334 amino acid sequence alterations within SEQ ID NO:1 from position 148 through position 843, inclusive - satisfying a statistical limitation of 52% identity over both the heavy and light chain regions - whereby amino acid insertions, deletions, or substitutions might occur anywhere, in any combination or any pattern, in the mature protease amino acid sequence of 696 amino acids set forth in SEQ ID NO:1. Mere sequence perturbation cannot enable the design and preparation of nucleotide sequences encoding the myriad of divergent proteases embraced by the claims and provide the public with a protease that retains the claimed specificity. The standard set by the CCPA, the precursor of the Court of Appeals for the Federal Circuit, is not to "make and screen" any and all possible alterations because a reasonable

correlation must exist between the scope asserted in the claimed subject matter and the scope of guidance the specification provides. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 25 (CCPA 1970) (enablement varies inversely with degree of unpredictability of factors involved in physiological activity of peptide hormone); **see also**, *Ex parte Maizel*, 27 USPQ2d 1662, 1665 (Bd. Pat. App. & Int. 1992) (functional equivalency of divergent proteins unsupported by disclosure of single B-cell growth factor allele). The Federal Circuit approved the CCPA's standard in *Genentech, Inc. v. Novo-Nordisk A/S*, 42 USPQ2d 1001 (Fed. Cir. 1997). Applying the "*Forman*" factors discussed in the communication mailed July 2, 2003, to Applicant's disclosure, it is apparent that:

a) the specification lacks adequate, specific, guidance for altering the amino acid sequence of the native protease of SEQ ID NO:1, from position 148 through position 843, inclusive, to the extent recited in the claims,

b) the specification lacks working examples wherein the amino acid sequence of the native protease of SEQ ID NO:1, from position 148 through position 843, inclusive, is altered to the extent recited in the claims,

c) in view of the prior art publications of record herein, the state of the art and level of skill in the art do not support such alteration, and,

d) unpredictability exists in the art where no one has specifically identified even a few amino acids for concurrent modification in members of the class of cysteine proteases represented by the amino acid sequence of SEQ ID NO:1.

Thus, the rejection of record of claims 1, 2, 4-9, 19, 21-23, 25-27, and 29 is sustained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is now 571.272.0933. The examiner can normally be reached between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Ponnathapura Achutamurthy, can now be reached at 571.272.0928. The fax phone numbers for all communications for the organization where this application or proceeding is assigned remains 703.872.9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is now 571.272.1600.

William W. Moore
April 2, 2004

NASHAAT T. NASHED PH.D.
PRIMARY EXAMINER